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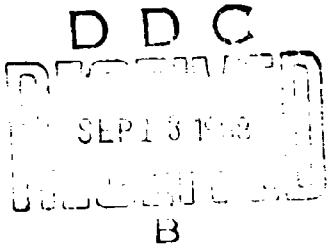


DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

EXPERIMENTAL HYPERGLYCAMIA IN FEVER

Hans Cohn

Zeitschrift für die gesamte experimentelle Medizin (Journal for All Experimental Medicine), Vol 53, 1927, pages 878-882

(Submitted on 9 September 1926)

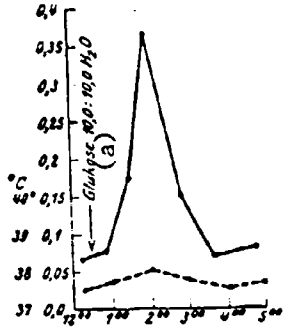
The investigations of Rosenthal, Licht, and Freund have added an important finding to the already known close relationship between carbohydrate metabolism and fever susceptibility in the warm-blooded organism: an animal rendered hypoglycamic by insulin is made feverish neither by infectious agents nor by fever-arousing substances (e.g., adrenalin, tetrahydronaphthylamin). "A certain increase" in sugar concentration in the tissues appears necessary for fever-susceptibility. (/Note/ "Insulin und Wärmeregulation" /Insulin and Regulation of Heat/, Arch. f. exp. Pathol. u. Pharmakol., 103, 1924.)

The closely related question concerning the behavior of sugar concentration during fever has often been investigated. (/Note/ Freund and Marchand, "Über Blutzucker und Wärmeregulation" /On Sugar in the Blood and Temperature Regulation/, loc. cit., 73, 1913; with additional citations.) Despite the often confirmed rise in sugar in the blood during fever, these tests have revealed no regularities between degree of fever and sugar level; hence Freund's conclusion that fluctuations in sugar level depend not on fever but on "the degree of intoxication and especially the toxic damage to the liver." (/Note/ "Über Wärmeregulation und Fieber" /On Regulation of Temperature and Fever/, Ergebn. d. inn. Medizin u. Kinderheilk., 22, 1922.)

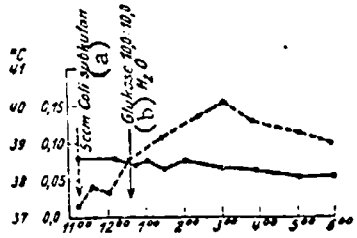
The test method consisted ordinarily of a single determination of blood-sugar in various illnesses with febrile course, e.g., pneumonia, typhus, nephritidis, etc.

It therefore seemed important to apply the method of the continuous curve after alimentary burdening, as they are used to provide pictures in diabetes and Graves' disease, in order to clarify the relation between fever and sugar metabolism. As Freund and Marchand properly warn, blood-sugar changes tell nothing about sugar consumption but only about the relation between consumption and carbohydrate mobilization. Thus, the fate of a known quantity of sugar -- at least partial knowledge thereof -- could afford better conclusions about consumption.

The test procedure was as follows: rabbits with fixed blood-sugar levels were subjected to fever by injection of pyrogenous substances -- the most suitable being dead 48-hour old Coli-Bouillon cultures. After a certain time the animals received a fixed amount of glucose. Then half-hour blood samples were taken and the albumen removed from the blood. Temperature was taken on the same schedule. Sugar content was measured by the Bang method.



Curve 1. Blood-sugar level in rabbits after glucose injection at normal temperature.
Weight: 2000 g
Legend: (a) Glucose

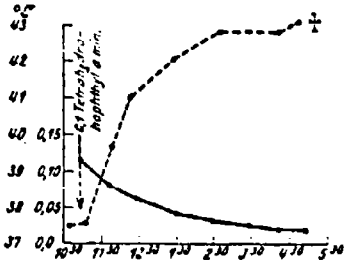


Curve 2. The same at fever temperature (Coli-injection).
Weight: 2100 g.
Legend: (a) Coli-subcutaneous
(b) Glucose

Whereas the sugar curve of the control animals, which had received no Coli-injection and had normal temperature fluctuations, showed an immediate steep rise, reaching its apex after about two hours, and then fell just as sharply (see Curve 1 as a typical example), the curve for feverish animals was quite different. Without any clear rise the curve held the same level with but minor fluctuations and then sank after several hours of fever, usually falling gradually below the initial level.

Occasionally there was an indication of a rise in the curve, especially with animals whose temperature did not rise at the desired rate and to the desired level. On the other hand, the temperature of some control animals

began to rise without fever-arousing means when they resisted mechanical feeding; in these cases the typical steep curves were less clear. These complementary findings indicate a direct relationship between the two factors, temperature and sugar level. Toxic damage to the liver, which certainly influences the blood-sugar and thus distorts the picture in Freund's sense when fever is of longer duration, is of lesser importance at the beginning of fever.



Curve 3. Temperature and blood-sugar curve in rabbits infected with tetrahydronaphthylamin. Weight: 4300 g.

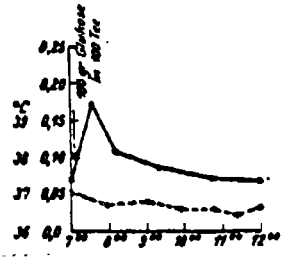
In consonance with Freund and Grafe, the blood-sugar at febrile temperature and without alimentary burden showed no typical behavior despite some deviations from the norm. An interesting exception was formed by the tests with β-tetrahydronaphthylamin as fever-arousing agent, a means that had to be abandoned because of the resulting change in blood distribution and the strong vasoconstriction in the periphery.

In these tests the blood-sugar began to sink with rising temperature, and continued to drop throughout the motor disturbances and cramps which led to death (see Curve 3). The clinical picture -- disturbance leading to serious cramps while sugar-level was falling well below the norm -- suggested comparison with insulin poisoning. But the third symptom, falling temperature, was missing, for the animal died in hyperpyrexia (43° C.!). The connection between hypoglycamia and cramps, ascertainable with other cramp-producing substances, could be more than accidental however.

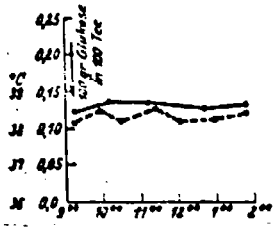
Since tests on animals, particularly blood-sugar measurements, are not necessarily applicable to the human organism, we made another series of tests by the same procedure on patients with various infections. One hundred g of glucose dissolved in tea as it is given to test liver functioning was usually taken without resistance.

Curve 4 shows the well-known physiological sugar level of a healthy person after administration of 100 g glucose.

Curve 5 gives the picture of the feverish organism, corresponding to the animal tests, under the same conditions. But not all of our curves were as unambiguous as these, for the differences occasioned by relatively large doses given the animals were more clearly manifested, and also the relationships were complicated because the patients with fever had had their illnesses for some time.



Curve 4. Sugar curve in human at normal temperature after 100 g glucose.



Curve 5. The same with fever (facial erysipelas).

Various theoretical possibilities emerge from the findings. The simplest assumption, since carbohydrates are known to meet increased requirements first and with greatest ease, is that with the gradual rise in energy consumption during fever the ingested sugar is applied so quickly and directly to energy production that there is no significant post-resorptive increase of glucose in the blood. Perhaps changes of fermentative types are decisive for the unequal results with ingested glucose at normal and febrile temperatures (compare the cited connection between insulin and heat!).

Richard May provided evidence that, with rising energy needs of the fevered organism, the glycogen supply is quickly used, a finding that accords well with our experience. And the advice of experienced clinicians to nourish fevered patients with quantities of carbohydrates finds herein at least a partial theoretical basis. (/Note/ Proceedings of the 30th Congress of Internal Medicine, Wiesbaden, 1913, with remarks by Müller.)

Summary

Animal as well as human tests show that in the fevered organism the blood-sugar curve rises little or not at all after peroral ingestion.

The explanation is to be sought in terms of the general rise in energy requirements during fever, an increase met first and easiest by carbohydrates. (/Notes/ Freund and Grafe, "Über das Verhalten des Blutzuckers im Fieber" /On the Behavior of Blood-Sugar during Fever/, Arch. f. klin. Med., 110, 1913, with additional citations; Rolly and Oppermann, "Das Verhalten des Blutzuckers bei Gesunden und Kranken" /The Behavior of Blood-Sugar in Healthy and Sick Persons/, Biochem. Zeitschr., 48, 1913.